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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,655	12/05/2003	Istvan Szelenyi	6319-1814	8949

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,655	SZELENYI ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-27* is/are pending in the application.

4a) Of the above claim(s) *16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 02/15/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgment is made of applicant's filing of an amendment filed 02/15/2007. By the amendment, claims 12-15 and 24-25 have been amended and claims 26-27 have been newly added.

2. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 12 and 23-27 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the specific sodium channel inhibitor (e.g., tolperisone, eperiosone, eperisone and silperisone), does not reasonably provide enablement for "sodium channel inhibiting substance". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention is drawn to a method of treating neuralgia pain comprising administering a combination of retigabine and a sodium channel inhibiting substance.

The breadth of the claims is very broad due to plethora of compounds having characteristics of "a sodium channel inhibiting substance". The claimed "a sodium channel inhibiting substance" encompasses not only inhibitor of sodium channel including various subunits of voltage-gated sodium channel (e.g., β1-4 subunits) and non-voltaged gated sodium channel but also inhibitors or partial antagonists of sodium channel including sodium/hydrogen exchangers, sodium-glucose transporters, sodium/myoinositol cotransporter, Na+/I- symporter, sodium/potassium/calcium exchanger, Na+/K+/Cl- cotrasporter and etc…

The relative skill of those in the pharmaceutical art and the unpredictability of the pharmaceutical art are very high. One having ordinary skill in the art would have not known that various classes of compounds encompassed by the instant invention would behave similarly under the instantly claimed condition. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

To practice the instant invention to the claimed scope, applicant would have to screen numerous possible compounds characterized as "a sodium channel inhibiting or –influencing substance" considering the structure-activity relationship of the compounds and then test compounds and extrapolate results to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Although the specification describes tolperisone, eperisone, silperisone, riluzole, prpafenone, lidocaine, flecainide and metixen as suitable "a sodium channel inhibiting substance", there is no teaching in the specification that any other compounds having inhibiting activity of sodium channel including "sodium/hydrogen exchangers, sodium-glucose transporters, sodium/myoinositol cotransporter, Na+/I- symporter, sodium/potassium/calcium exchanger, Na+/K+/Cl- cotrasporter" would have similarly as the exemplified compound. In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art where many specific differences or different physicochemical properties are existed among unrelated structural compounds would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 14-15, the claims recite "other tolperisone analogs". It is not clear what "other tolperisone analogs" refers to. The specification does not define the term and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

For the examination purpose, the term "other tolperisone analogs" is interpreted as "eperisone and silperisone".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 12-13 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rundfeldt et al. (US 6117900) in view of Cai et al. (US 6281211), and further in view of the applicant's admitted prior art of the record (page 1, line 25 through page 4, line 3).

Rundfeldt teaches the use of retigabine for the treatment of neuropathic pain, wherein said compound is administered in various dosage forms including oral or parenteral forms (abstract; column 8, lines 26-37; claims).

Cai is being supplied as reference to demonstrate the routine knowledge in using Na+ channel blocker such as riluzole, lidocaine, propafenone and semicarbazone derivatives for the treatment neuropathic pain (see particularly "Related Background Art" in column 1, lines 18-56 and "Summary of Actions"; abstract).

Applicant's admitted prior art of records teaches the use of sodium channel inhibitor or tolperisone in normalizing or maintaining muscle tone (spasticity).

The teaching of Rundfeldt differs from the claimed invention in the combination use of retigabine and sodium channel blocker such as lidocaine, propagenone and riluzole. To incorporate such teaching into the teaching of Rundfeldt, would have been obvious in view of Cai who teaches the use of sodium channel blocker such as riluzol, lidocaine and propagenone for the treatment of neuropathic pain.

Above references in combination make clear that retigabine and sodium channel blocker such as lidocaine, propageneone and riluzole have been individually used for the treatment of neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character

is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

With respect to the determination of various dosage forms (e.g., orally, rectally, intravenously, transdermally, subcutaneously or intracutaneously) and the current administration regimen of two drugs (e.g., simultaneously, separately or consecutively), such determination of appropriate dosage forms and administration regiment for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of drug delivery information provided in the prior art references.

With respect to "said neuralgia pain or neuropathic pain is accompanied by an increase in muscle tone" in claims 26 and 27, the prior art reference(s) does/do not specifically mention the feature of the presence of "an increase in muscle tone" in the prior method. However, one having ordinary skill in the art would have expected at the time of the invention was made that such feature of the instant invention would have been characteristic of the modified prior art method. Especially, considering the state of art knowledge at the time of the invention was made as evidenced by the applicant's admission, one having ordinary skill in the would have expected that the administration of the instant combination containing sodium channel inhibitor would benefit the patient suffering from neuropathic pain accompanying with the increase in muscle tone (spasticity). Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

6. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rundfeldt et al. (US 6117900) in view of Cai et al. (US 6281211), and further in view of the applicant's admitted prior art of record (page 3, lines 11-23).

The modified teaching of Rundfeldt (Rundfeldt in combination with Cai) includes all that is recited in the claims 14 and 15 except the use of "tolperisone, eprisone and silperisone".

The admitted prior art of record teaches tolperisone as sodium channel blocker similar to lidocaine.

One having ordinary skill in the art would have expected that tolperisone would behave similar as to the known sodium channel blocker such as lidocaine and provide therapeutic utility in the treatment of neuropathic pain through sodium channel blocking mechanism. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Response to Arguments

7. Applicant's arguments filed 02/15/2007 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that sodium channel inhibitor constitutes a class of materials that is well known in the art. Applicant alleges that based on the eight examples provided in the specification and the state of art, the specification provides enabling disclosure for the term "sodium channel inhibiting substance".

This argument is not considered persuasive. It is generally recognized in the art that biological compounds often react unpredictably under different circumstances (Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)). In other words, it is generally known that not all of sodium channel inhibitors are known to behave similarly (see Touboul et al., "A Comparative Evaluation of the Effects of Propafenone and Lidocaine on Early Ventricular Arrhythmias after Acute Myocaridal Infarction", European Heart Journal, abstract, 1988, Vol. 9, No. 11, pp. 1188-1193). Touboul discloses that only lidocaine could suppress complex arrhythmia where propafenone is found not in favor of suppressing complex arrhythmia.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the examples provided in the instant specification to the larger and highly varied genera of compounds that are characterized by "sodium channel inhibitor", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking

experimentation study" to make/use the claimed "sodium-channel inhibiting substance" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Applicant's argument in the response takes the position that it is readily apparent to one of skill in the art what the term "tolperisone analogs" refers to, for example in light of the submitted USP 4181803 and USP 4528299.

This argument is not found persuasive. Unlike the applicant's argument, the instant specification does not clear define the term, nor provides any examples of "other tolperisone analogs" other than eperisone and silperisone. Especially, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompasses a myriad of possibilities, the skill artisan should doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the prior art references in combination (Rundfelt and Cai) make clear that retigabine and sodium channel blocker such as lidocaine, propageneone and riluzole have been individually used for the treatment of neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active

ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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